EXHIBIT C

NCDENR
North Carolina Department of Environment and Natural Resources
Division of Air Quality

Beverly Eaves Purdue
Governor

Sheila C. Holman
Director

Dee Freeman
Secretary

August 10, 2012

MEMORANDUM

TO: Charles Wakild, Director
Division of Water Quality

THROUGH: Sheila Holman, Director,
Division of Air Quality

FROM: Robin Barrows, Acting Liaison,
Secretary's Science Advisory Board on Toxic Air Pollutants (NCSAB)

SUBJECT: NCSAB Recommendation for the Revision of the IMAC for Perfluorooctanoic Acid (PFOA)

Attached is the completed risk assessment of PFOA by the NCSAB requested by DWQ. The NCSAB recommends, by a unanimous vote of the membership, an Interim Maximum Allowable Concentration (IMAC) for PFOA in the range of 1.1 – 1.6 µg/L (ppbv). A critical endpoint (liver-to-brain weight ratio) was chosen based on animal toxicology studies. These recommendations are summarized as follows:

Key Study	POD, µg/mL	Exposure Level[a], µg/person-day	UF	IMAC estimate[b], µg/L
Butenhoff, 2004 (rat)	58	487.2	30	1.6
Butenhoff, 2002 (monkey)	40	336.0	30	1.1

a. **Exposure Level = Point of Departure (µg/mL) x 0.12 µg ingested/kg/µg/mL x 70 kg/person. The 0.12 µg ingested/kg/µg/mL factor is from Clewell et al., 2006**
b. **IMAC Estimate = (Exposure Level/UF) x 0.2/2 L/person-day. A Relative Source Contribution factor of 20% (0.2) and a daily consumption factor of 2L were used**

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Recommendation to the Division of Water Quality for an Interim Maximum Allowable Concentration for Perfluorooctanoic Acid (PFOA) in Groundwater

Executive Summary

The North Carolina Division of Water Quality (DWQ) requested the assistance of the North Carolina Secretary's Science Advisory Board on Toxic Air Pollutants (NCSAB) in reviewing the toxicological literature on perfluorooctanoic acid (PFOA) and recommending to DWQ updating the Interim Maximum Allowable Concentration (IMAC) for PFOA in groundwater.

Because of releases of perfluoroalkyl acids (PFAAs) to the environment reported in other states, there is growing public concern over the manufacture and use of PFOA at a production facility in Fayetteville, NC. Understanding this concern, in 2006 the North Carolina Division of Water Quality (DWQ), in consultation with the North Carolina Division of Waste Management (DWM) and the North Carolina Department of Health and Human Services (DHHS), established an IMAC of 0.002 mg/L (2 µg/L (ppbv)) for PFOA. This temporary health-based level was developed using applicable state regulations and published, peer-reviewed toxicological data and was intended for the protection of groundwater as a source of drinking water.

This report summarizes the NCSAB review of PFOA and details the process by which the NCSAB makes its recommendation. Based on the current toxicological literature and discussions that the NCSAB had with research scientists conducting research on the health effects associated with exposure to PFOA, the NCSAB recommends that the IMAC be reduced to 1 µg/L (ppbv).

Background Information

Perfluorooctanoic acid (PFOA) (CAS No. 335-67-1) is a perfluoroalkyl acid (PFAA) having the structure shown in Figure 1.

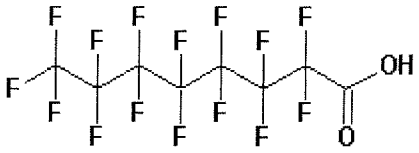

FIGURE 1 – Structure of PFOA

PFAAs are anthropogenic, and their use is relatively new, occurring only over the past half-century. The Carbon-Fluoride bonds in PFAAs make them stable at high temperatures. Chemical and physical properties make PFAAs prime candidates for use not only in surfactant manufacture, but also in protective coatings for a wide range of products, including clothing and paper.

In 2002, The DuPont De Nemours-Fayetteville facility (DuPont-Fayetteville) began manufacturing ammonium perfluorooctanoate (APFO), the ammonium salt of perfluorooctanoic acid. The facility is located in the lower segments of Cape Fear River Basin. Prior to this date, the plant neither produced nor used APFO in its manufacturing processes. Heightened public concern over possible adverse health effects resulting from environmental release of PFOA caused DWQ, in consultation with DWM and the DHHS, to establish an "Interim Maximum Allowable Concentration" (IMAC) of 2 µg/L (2 ppbv) for PFOA in 2006. This temporary health-based level was developed using applicable state regulations and published, peer-reviewed toxicological data and was intended for the protection of groundwater as a source of drinking water.

DWQ requested assistance from the North Carolina Secretary's Science Advisory Board on Toxic Air Pollutants (NCSAB) to review the toxicological and epidemiological literature relating to PFOA and recommend to DWQ an updated IMAC.

In 2002, groundwater samples at the DuPont-Fayetteville facility began to be collected; confirmatory groundwater samples were collected in early 2003. APFO was detected in the parts-per-trillion (ppt or ng/L) range in these samples. In June 2003, the Fayetteville production facility reported APFO in groundwater to the North Carolina Department of Environment and Natural Resources (NCDENR) as the discovery of a new chemical in the groundwater.

This facility has since installed and sampled 39 temporary and permanent monitoring wells on-site. APFO concentrations exceeding the current IMAC have been reported for three of the wells. The facility has also sampled nine off-site private groundwater wells. These wells are located near the APFO manufacturing unit. APFO concentrations were below the limit of detection in eight of the nine off-site wells. Two groundwater samples were collected at the ninth well: one sample was non-quantifiable for APFO; the second sample was reported to be 0.011 µg/L (0.011 ppb). Additionally, at the request of NCDENR, US EPA Region 4 staff observed a sampling event conducted by the facility in which groundwater, surface water, and sediment samples were collected. These samples were split between the US Environmental Protection Agency (USEPA) and the facility. The USEPA National Enforcement Investigations Center and National Exposure Research Laboratory analyzed the EPA samples. The analytical results were reported in 2006 and were consistent with those reported by the production facility.

Data suggest the sources for APFO in groundwater at the facility are two surface impoundments and the APFO manufacturing unit. The twin surface impoundments contain water from the Cape Fear River that supplements the facility non-potable water supply. The concentrations of APFO in groundwater samples collected in the area of the two surface impoundments are similar to the concentrations reported by the facility and the USEPA for the Cape Fear River. The greatest concentrations of APFO in groundwater at the site have been reported in a perched aquifer zone beneath the APFO manufacturing unit. Monitoring wells screened in this zone, which appear to

have impacted the aquifer below it, are frequently dry. The facility plans to conduct investigations that will better define the relationship between the shallow perched zone, the deeper aquifer, and the distribution of APFO in the groundwater. These investigations will be conducted under NCDENR oversight. Currently, the production facility collects annual samples of the groundwater for APFO. Analytical results are reported to both the North Carolina Division of Waste Management (NCDWM) and the USEPA.

In the spring of 2006, the USEPA National Exposure Research Laboratory (Nakayama, Strynar, Helfant, Egeghy, Xibiao & Lindstrom, 2007) conducted a study of PFAAs in the surface waters of the NC Cape Fear River Basin. One hundred samples from 80 different locations were collected. While the watershed is principally rural and agricultural in nature, possible sources of PFOA were noted to include: use of fire-fighting foams, metal-plating facilities, textiles, and paper production. 82% of samples taken indicated PFOA levels above the LOQ (limit of quantification, 0.001 μg/L). PFOA concentrations greater than 0.040 μg/L were reported for 26 sites (32%). The maximum concentration of 0.287 μg/L was observed from samples taken from the Haw River.

Sources of Human Exposure

PFOA appears to be ubiquitous in the environment. Lau et al. (2007) (Lau, Anitole, Hodes, Lai, Pfahles-Hutchens & Seed, 2007) reports PFOA detected globally in surface waters, air, sludge, soils, sediments, and ice caps.

Generally, PFOA concentrations are in the parts-per-trillion (ppt) range in drinking water. Similar results have been reported in 9 major freshwater lakes and rivers throughout New York State (Sinclair,et al, 2006), where median PFOA levels ranged from 0.014 to 0.049 μg/L with a maximum of 0.173 μg/L. In Alabama(Hansen, Johnson, Eldridge, Butenhoff & Dick, 2002), PFOA levels are below 0.025 μg/L in the Tennessee River upstream of the discharge site of a fluorochemical production facility. After a 10-km mixing distance downstream of the discharge, the PFOA concentration averaged 0.394 μg/L, with relatively little variation in the data. Emmett (Emmett, Shofer, Zhang, Freeman, Desai & Shaw, 2006b) reported a mean PFOA concentration of 0.035 μg/L in drinking water in the vicinity of a production plant in West Virginia.

A review of the literature reveals that assessments of human exposure to PFOA are largely related to an ingestion route of exposure. Additionally, exposure assessments have been reported for air, water, and food, as well as house dust. Fromme (Fromme, Midasch, Twardella, Angerer, Boehmer & Liebl, 2007a; Fromme, Tittlemier, Völkel, Wilhelm & Twardella, 2009) reported an estimated average daily intake of PFOA for an adult population in southern Bavaria of 2.9 ng/(kg body weight) with the major contributor being food. Trudel (Trudel, Horowitz, Wormuth, Scheringer, Cousins & Hungerbuhler, 2008) reported modeled long-term daily intake of PFOA in the general populations of the U.S. and Europe to range from 1 to 130 ng/(kg body weight). Strynar (Strynar & Lindstrom, 2008) reported the PFOA concentration in dust samples collected from homes (n =

102) and day-care centers (n = 10) in Ohio and North Carolina in 2000-2001. PFOA was detected in over 95% of the samples at a median concentration of 142 ng/g of dust (95th percentile = 1960 ng/g). Kato (Kato, Calafat & Needham, 2009) reported a median concentration of about 90 ng/g PFOA in 10 house dust samples collected in 2004 in Atlanta, GA.

Washburn (Washburn et al., 2005) examined PFOA concentrations in various consumer and commercial products, ranging from fabrics, textiles, and carpeting, to floor waxes, paint, and cleaners. Washburn estimated average PFOA intake for children and adults. It was concluded that exposure to PFOA from carpeting and/or textiles is minor.

PFAAs have been measured in the general human population since around the year 2000. PFAA levels have been measured in those occupationally exposed over a longer time period. Lau (Lau et al., 2007) reported levels of PFOA in the occupationally exposed are approximately one order of magnitude higher than in the general population. The table in Appendix 1, extracted from (Lau et al., 2007) shows the range of PFOA in human fluids: serum, plasma, whole blood, and breast milk.

Hölzer (Hölzer et al., 2009b), reported that PFOA was detected in the drinking water of Arnsberg, Germany in 2006 at levels between 500-640 ng/L. Soon after detection, charcoal filters were installed, reducing the PFOA concentration to below the limit of detection. Blood plasma samples were collected from residents in 2006 and repeated after a one-year interval (see Table 1).

Table 1 – Reported Levels of PFOA in Blood Plasma Samples in Holzer et.al. Data

Demographic	Blood Plasma PFOA, 2006 µg/mL (GM)	Blood Plasma PFOA, 2007 µg/mL (GM)	% Reduction in Blood Plasma Concentration
children	22.1	17.4	21.2
mothers	23.8	18.8	21.0
men	25.7	23.4	8.9

(GM : geometric mean)

Steenland (Steenland, Fletcher & Savitz, 2009a) reported a study to determine the percent reduction in serum PFOA after institution of water filtering in two communities: Little Hocking, West Virginia and Lubeck, Ohio. 150 adults serviced by the Lubeck Public Service District and 50 adults serviced by the Little Hocking Water Association participated. Each participant was required to have a serum PFOA level ≥ 50 µg/L and to: have never been employed by the DuPont company; have never had any job in which PFOA was used; and have not grown vegetables at home during the study period. Participants were further subdivided into groups by primary source for drinking water: public water or bottled water. The Lubeck sample was followed for one year after water filtration began (June 2007 – June 2008); the Little Hocking sample was followed for three months prior to water filtration and for 6 months following. The results are shown in Table 2. The average rate of decrease in serum PFOA over all four groups was estimated to be 26%. Steenland, et. al.

estimated an average half-life serum PFOA from these data to be 2.3 years (95% CI: 2.1 – 2.4 years).

Table 2 – Reported Reduction in Serum PFOA Concentration Level After Water Filtering (from Steenland et.al.)

Community	Average Decrease in Serum PFOA Level, ng/L (% Decrease), Public Water	Average Decrease in Serum PFOA Level, ng/L (% Decrease), Bottled Water
Lubeck, OH	32 ng/L (26%) (n = 130)	16 ng/L (28%) (n = 17)
Little Hocking, WV	39 ng/L (11%) (n = 39)	28 ng/L (21%) (n = 11)

Tardiff (Tardiff et al., 2009) summarized human exposure data, stating that of all routes of exposure, diet appears to be a major contributor to body burden, and that intake rates vary from about 1 ng/kg body weight-day for consumers not living near a PFOA production facility to about 300 ng/kg body weight-day for consumers living near a production facility.

Serum levels have been reported for occupational exposure to PFOA. Sakr (Sakr, Kreckmann, Green, Gillies, Reynolds & Leonard, 2007b; Sakr, Leonard, Kreckmann, Slade & Cullen, 2007a) reported a study of employees at the DuPont Washington Works facility in WV. Similar studies have been conducted at 3M facilities in Cottage Grove, MN, Decatur, AL, and Antwerp, Belgium (Olsen & Zobel, 2007b). The findings of these studies are summarized in Table 3.

Table 3 – – Reported Levels of Serum PFOA in Selected Occupational Studies

(ND: non-detected)Company	Range (mg/L)	Reference
DuPont – Washington Works	ND – 26	(Sakr et al., 2007b; Sakr et al., 2007a)
3M – Cottage Grove	0.01 – 92.03	(Olsen et al., 2007b)
3M – Decatur	0.04 – 12.7	(Olsen et al., 2007b)
3M – Antwerp	0.01 – 7.04	(Olsen et al., 2007b)

Metabolism and Kinetics of PFOA

An excellent review of the pharmacokinetics of PFOA is found in Lau (Lau et al., 2007). It has been demonstrated in numerous animal studies that PFOA is rapidly absorbed, not metabolized, and undergoes extensive enterohepatic circulation (Davis, Vanden Heuvel, Kuslikis & Peterson, 1991; Goecke, Jarnot & Reo, 1992; Kemper & Jepson, 2003; Kemper & Nabb, 2005; Kuslikis, Vanden Heuvel & Peterson, 1992). Urinary excretion is the predominant route of elimination, and it has been demonstrated that there are significant differences in PFOA elimination through urinary excretion both among humans and between humans and animals (Andersen, Clewell, Tan, Butenhoff & Olsen, 2006; Butenhoff et al., 2004a; Harada, Inoue, Morikawa, Yoshinaga, Saito & Koizumi, 2005a; Kemper et al., 2003; Kudo, Katakura, Sato & Kawashima, 2002). Once absorbed, PFOA is distributed to the serum, kidney, and liver (Hundley, Sarrif & Kennedy, 2006; Johnson,

Gibson & Ober, 1979). Apelberg (Apelberg et al., 2007a) reported detectable levels of PFOA in umbilical cord blood, indicating PFOA can cross the placental barrier.

The serum elimination half-life of PFOA has been reported for several animal species and humans, as in Table 4.

Table 4 – Summary of Reported Serum Elimination Half-Life of PFOA

Species	Sex	Elimination Half-Life	Reference
Rat	Male Female	4-6 days 2-4 hrs	(Johnson et al., 1979; Kemper et al., 2003)
Mouse	Male Female	19 days 17 days	(Kudo et al., 2002)
Monkey, cynomolgus	Male Female	21 days 30 days	(Butenhoff et al., 2004a)
Dog	Male Female	20-30 days 8-13 days	(Hanhijarvi, Ylinen, Haaranen & Nevalainen, 1988)
Human	both	3.5 yr (GM*) 3.8 yr (AM**)	(Olsen et al., 2007)
	both	2.3 yr	(Steenland et al., 2009a)

*GM = Geometric mean
**AM = Arithmetic mean

Lau (Lau et al., 2007) reported that since differences in elimination within species (gender) and between species is not well understood, in order to compare toxicological effects, a body burden metric must be used instead of administered dose. Differences in renal transport mechanisms may account for the differences that have been observed within and between species. It had been hypothesized that humans have long elimination half-lives because the glomerular filtration rate can be as much as 5-fold greater than the renal clearance of PFOA suggesting the absence of active excretion in the kidney (Harada et al., 2005a). Andersen (Andersen et al., 2006) suggests that efficient renal resorption explains reduced clearance in humans. Results reported using a pharmacokinetic model developed by Tan (Tan, Clewell & Andersen, 2008), seem to support this hypothesis.

Clewell (Clewell, Tan & Andersen, 2006) scaled an existing monkey model and calibrated it to match a human elimination half-life of 4.4 years by increasing the resorption rate of PFOA from urinary filtrate by a factor of 7. Andersen (Andersen et al., 2006) reported that on the basis of the output from this model, the long human elimination half-life results from more efficient resorption of PFOA by the kidney. Lou (Lou et al., 2009) used a saturable resorption model (like that of Andersen) and found that the model satisfactorily described mouse serum data.

Animal Studies

There are extensive reviews on PFOA toxicity published in the peer-reviewed literature (Kennedy, Butenhoff & Olsen, 2004; Lau et al., 2007; Lau, Butenhoff & Rogers, 2004). In addition, the US EPA has issued a draft risk assessment on PFOA (US EPA, 2005).

Acute Studies

The results of several studies on acute toxicity are summarized in Table 5.

Table 5 – Summary of Reported Acute Toxicity Data of PFOA in Animal Studies

Animal System	Metric	Dose	Reference
Sherman-Wistar rats	Oral LD_{50}	Male: <1000 mg/kg Female: <1000 mg/kg	(Gabriel, 1976)
CD rats	Oral LD_{50}	Male: 680 mg/kg Female: 430 mg/kg	(Dean & Jessup, 1978)
Sprague-Dawley rats	Inhalation – No mortality	Male: 18.6 mg/L, 1 hr. Female: 18.6 mg/L, 1 hr.	(Rusch, 1979)
New Zealand white rabbits	Dermal LD_{50}	Male: >2000 mg/kg Female: >2000 mg/kg	(Glaza, 1995)
Sprague-Dawley rats	Oral LD_{50}	Male: >500 mg/kg Female: 250 – 500 mg/kg	(Glaza, 1997)

Subchronic Studies

Subchronic exposure studies in animals are also summarized in Table 2 of (Tardiff et al., 2009), that is also reproduced in Appendix 2. Studies demonstrate that in rodents the liver is the primary target organ for toxicity, irrespective of the route of exposure. Increased liver weight accompanied by hepatocellular hypertrophy is commonly observed. At doses ≥30 ppm, liver degeneration and necrosis are observed as are increases in serum liver enzymes. Increased liver weight and hepatocellular hypertrophy is observed to occur in the rodent through a PPARα-activation mechanism. Klauning (Klaunig et al., 2003) has described the key events in the PPARα-agonist mode of action (MOA) in the rodent. Kudo (Kudo, Mizuguchi, Yamamoto & Kawashima, 1999) observed that rats that were fed PFOA showed decreased serum cholesterol and triglyceride levels. It has been noted that this is also seen in the use of hypolipemic drugs that are PPARα agonists. In cynomolgus monkeys, increased liver weights with exposure to PFOA are also observed; however, the reason for the increase appears to be different than for that in rodents. It is possible that in monkeys, hepatocelluar hypertrophy may be the causative factor in increased liver weight.

Chronic/Cancer Studies

The effects of chronic exposure to PFOA have been evaluated in two rat studies: Sibinski (Sibinski, 1987) and Biegel (Biegel, Hurtt, Frame, O'Connor & Cook, 2001).

The Sibinski Study

Groups of 50 male and 50 female Sprague-Dawley rats (Crl:CD BR) were fed diets containing 0, 30 or 300 ppm APFO (ammonium perfluorooctanoate) for two years. An additional group consisting of 15 males and 15 females were fed diets of 0 or 300 ppm APFO and sacrificed and evaluated at one year. Mean male rat APFO consumption was 1.3 and 14.2 mg/kg-day for the 30 and 300 ppm groups, respectively. Mean female rat APFO consumption was 1.6 and 16.1 mg/kg-day for the 30 and 300 ppm groups, respectively. All animals were observed daily over the entire study period. Body weights and feed consumption were recorded weekly for the first six months of the study, then biweekly thereafter through the end of the study period. For groups of 15 rats per sex at intervals of 3, 6, 12, 18, and 24 months, pathological examinations, including hematology, serum chemistry, and urinalysis were conducted. Postmortem examinations were performed on animals that died during the study as well as those sacrificed during and at the conclusion of the study. As part of the postmortem examinations conducted at the interim sacrifice and, additionally, for the two-year necropsies, 15 randomly selected rats per sex were selected from among the control and high exposure groups and weights of kidneys, liver, heart, spleen, testes, brain, adrenal glands, and uterus were recorded. Microscopic examinations were also performed for the control and high exposure groups.

Compared with the control group, there was a dose-related decrease in weight gain in male rats, and, to a lesser extent, in females; the decreases were statistically significant in the high-dose groups of both sexes. Since feed consumption was increased over the test period, the observed decreases were concluded to be treatment-related. No differences were observed in survival rates over the two-year study between treated and untreated groups.

A dose-related increase in ataxia was observed for female rats, generally observed in moribund animals. High dose males and females had significant decreases in erythrocytes, hemoglobin concentrations, and hematocrits compared to controls. Other slight, but statistically significant, increases in clinical chemistry were observed in both treated male groups from 3-18 months, but only in high-dose males at 24 months. Increases (up to around 10%) in liver and kidney weights were observed in both high-dose males and females at both the one year interim sacrifice and at the final necropsy; only the relative liver weight (vs. body or brain weight) increase in high-dose males was statistically significant.

Lesions in the liver, testes, and ovaries were observed on histological examination. Liver lesions were statistically significant only in the male high-dose group. Interim sacrifice histology showed that incidence of diffuse hepatomegalocytosis, portal mononuclear cell infiltration, and hepatocellular necrosis increased in high-dose males (compared to controls), as did the incidence of hepatocellular vacuolation in high-dose females (compared with controls). At the two-year

sacrifice, megalocytosis incidence was observed to be 0%, 12%, and 80% in males, and 0%, 2% and 16% in females (controls, low-dose, and high-dose, respectively). Hepatic cystoid degeneration was observed at 8%, 14% and 56% of males (controls, low-dose, and high-dose, respectively). Hyperplastic nodules were slightly increased (6%) in high-dose males vs. controls (0%).

At the one-year sacrifice, testicular lesions were observed in 6/50 high-dose and 1/50 low-dose rats (0/50 in controls). Aspermatogenesis was observed in 2/15 high-dose males (0/15 male controls). At the two-year sacrifice, testicular vascular mineralization was observed in 0%, 6%, and 18% of males (controls, low-dose, and high-dose, respectively). These observations were statistically significant in the high-dose group.

In female rats, a statistically significant dose-related increase in ovarian tubular hyperplasia incidence (0%, 14%, and 32% in controls, low-dose, and high-dose females) was observed at the two-year sacrifice. The slides of these ovaries were re-evaluated (Mann & Frame, 2004) (as cited in (US EPA, 2005)). The ovarian lesions were determined to be gonadal stromal hyperplasia and/or adenomas. No statistically significant increase in the total numbers of hyperplasias, adenomas, or both was observed in the treated groups compared to controls. Some evidence of an increase in stromal lesions was observed in the high-dose exposure group; however a greater incidence of adenomas was observed in the control group compared to either of the treated groups. Rats that died prior to or at the time of the one-year sacrifice were not considered at risk for tumor development.

It appears from these data that 300 ppm is the Maximum Tolerated Dose. A LOAEL of 300 ppm and a NOAEL of 30 ppm for male rats was established based on decrease in weight gain, increase in liver and kidney weights, and toxicity in the hematological and hepatic systems. For female rats a LOAEL of 300 ppm and a NOAEL of 30 ppm was established based on decreased body weight gain and hematological effects.

The Biegel Study

Biegel (Biegel et al., 2001) observed the induction of Leydig cell tumors in a two-year study of male Sprague-Dawley rats exposed at a dietary level of 300 ppm PFOA. There were 156 rats in the exposure group; 80 rats in the control group. Rats were weighed once per week during the first three months of the study and once biweekly for the remainder. Rats were sacrificed at intervals of 1, 3, 6, 9, 12, 15, 18 and 21 months. At each sacrifice, the liver and testes of 6 rats/group were weighed and evaluated for cell proliferation. An additional 6 rats/group were selected for peroxisome proliferation, and another 10 rats/group were selected for serum hormone analysis. All rats surviving to 24-months were sacrificed for microscopic examination of the heart, liver, testis, kidney, brain, and spleen.

In the treated group, statistically significant increases in relative liver weight and hepatic β-oxidation activity (compared to controls) were observed at all sacrifice times. Absolute testis weights were increased only at 24 months. No hepatic of Leydig cell proliferation was observed at any sacrifice time, and only an increase in serum estradiol concentration was observed in treated rats at 1, 3, 6, 9, and 12 months.

Biegel observed significant increases in: Leydig cell tumors (LCT) (0% controls, 11% treated); pancreatic acinar cell tumors (PACT) (0% controls, 9% treated); and liver adenomas (3% controls, 13% treated). One pancreatic cell carcinoma was observed in each of 76 treated rats and none in 80 controls. Sibinski reported no increase in PACT incidence and an incidence of pancreatic acinar hyperplasia of 0%, 6%, and 2% in controls, 30 ppm, and 300 ppm groups, respectively. The slides from both studies were independently re-evaluated and it was determined that exposure to PFOA produced increased incidences of proliferative pancreatic acinar cell lesions in both studies at 300 ppm. The differences in the two studies were thought to be due to the use of arbitrary diagnostic criteria and nomenclature.

Both the Sibinski and Biegel studies showed that PFOA induced liver adenomas, Leydig cell adenomas, and PACT in male Sprague-Dawley rats.

Animal Studies – Developmental/Reproductive

Developmental studies have been conducted using rabbits, rats, and mice (Abbott et al., 2007; Butenhoff, Kennedy, Frame, O'Connor & York, 2004b; Gortner, 1981; Gortner, 1982; Johansson, Eriksson & Viberg, 2009; Johansson, Fredriksson & Eriksson, 2008; Lau et al., 2006; Rosen, Thibodeaux, Wood, Zehr, Schmid & Lau, 2007; Staples, Burgess & Kerns, 1984; White et al., 2007b; White et al., 2009; Wolf et al., 2007). Effects observed in mice are different than those observed in the rabbit or rat (Dixon et al., 2012; Lau et al., 2006; Macon et al., 2011; White et al., 2011; Yang et al., 2009; Zhao et al., 2012). These studies show chronic exposure to PFOA is associated with developmental toxicity in rodents.

Butenhoff (Butenhoff et al., 2004b) reported the results of a two-generation reproductive toxicity study in Sprague-Dawley rats. Doses of 0, 1, 3, 10, or 30 mg/kg-day were administered orally. Decreased weight gain in the pups of pregnant rats exposed to 30 mg/kg-day of PFOA was reported. A statistically significant increase in mortality in both male and female pups as well as decreased body weight observed both after weaning and over the course of the study were reported.

Lau (Lau et al., 2006) reported dose-related fetal toxicity of PFOA in mice as well as early pregnancy loss, delayed fetal growth and development, and decreased post-natal survival.

In three studies (Macon et al., 2011, White et al., 2011, Zhao et al., 2012), mammary gland development in mice was evaluated following low dose exposure to PFOA. Macon et al. (2011) reported the results of prenatal PFOA exposure in CD-1 mice. Mice were dosed with 0, 0.3, 1.0, and 3.0 mg PFOA/kg/day (full gestation, gestational day [GD] 1-17) or 0, 0.01, 0.1, and 1.0 PFOA mg/kg/day (late gestation, GD 10-17). Stunted mammary gland development was observed in the offspring as assessed by developmental scoring at the lowest dose for both treatment regimens. Statistically significant reductions in longitudinal growth and fewer terminal end buds in mammary tissue occurred at postnatal day (PND) 21 in the late gestation group at 1.0 mg/kg compared to controls. In a similar study, White et al. (2011) reported the results of a three-generation developmental study in CD-1 mice. Exposure groups were dosed with 0, 1, or 5 mg PFOA/kg/day (GD 1-17); additional groups of dams were treated with 0 or 1 mg PFOA/kg/day throughout gestation and their F_1 and F_2 offspring received continuous 5 ppb PFOA in drinking water. The authors reported delayed mammary gland development occurred for both generations. Studies performed by Zhao et al. (2012) have shed additional light on the MOA of PFOA-induced effects on mammary development. Zhao reported that Balb/c mice were more sensitive to PFOA inhibition when compared with wild-type C57BL/6 mice. Accordingly, they exposed Balb/c to PFOA at 2.5 mg/kg/day while C57BL/6 wild-type or PPARα knockout mice received PFOA at 7.5 mg/kg/day. All mice were given PFOA by oral gavage 5 days per week for 4 weeks starting at 21 days of age. Similar to the work reported by Macon et al. (2011) and White et al. (2011) PFOA exposure in Balb/c and wild-type C57BL/6 mice was associated with altered mammary gland development as evidenced by reduced ductal length, decreased numbers of terminal end buds and stimulated ducts. Inhibition of mammary gland development was not observed in PFOA-treated C57BL/6 PPARα knockout mice suggesting the PPARα pathway is involved in PFOA inhibitory effect on the mammary gland. They also found that PFOA treatment at doses that inhibited mammary gland development was also associated with delayed or absent vaginal opening and lack of corpora lutea suggesting that estrous cyclicity was altered. Consistent with this theory, they found that supplementing mice with physiological levels of estrogen or progesterone reversed stunted mammary gland development in PFOA-exposed Balb/c and C57BL/6 wild-type mice.

In a uterotrophic study by Dixon et al. (2012), immature CD-1 mice were exposed to low doses of PFOA (0, 0.01, 0.1, or 1 mg PFOA/kg/day) on PND 18-20. They reported increased uterine weight on PND 21 at 0.01 mg/kg/day PFOA exposure, but other histopathologic changes were minimal.

Studies examining reproductive and developmental effects in rodents share certain - characteristics that limit their usefulness for quantitative risk assessment. These include small sample sizes, high plasma PFOA concentrations, and incomplete characterization of dose-response

relationships including the absence of a well defined NOAEL. One additional challenge is that the effect(s) seen, inhibition versus stimulation of mammary gland development for example, is influenced by the exposure dose and animal strain. Yang et al., (2009) reported that Balb/c mice exposed to PFOA (5 and 10 mg/kg) during the peripubertal period exhibited inhibition of mammary gland and uterine development, however, similarly exposed C57BL/6 mice exhibited stimulatory effects in both organs at the low dose (5 mg/kg) but inhibition at the higher dose (10 mg/kg). In addition, these diverging effects may not reflect serum PFOA concentrations. For example, Zhao and colleagues (2012) showed that Balb/c mice treated with 2.5 mg/kg of PFOA had plasma PFOA levels similar to that of wild-type C57BL/6 mice treated with 5 mg/kg of PFOA. Although similar plasma PFOA levels were seen opposite effects on mammary glands were observed.

Animal Studies - Immunotoxicity

Griffith (Griffith & Long, 1980) reported no histopathologic effects in the lymphoid, thymus, or bone marrow in a 90-day subchronic study in which Rhesus monkeys were exposed to PFOA at doses up to 10 mg/kg-day. Butenhoff (Butenhoff et al., 2002) reported no histopathologic effects in the spleen, thymus, or mesenteric lymph nodes in a 6-month subchronic study in which cynomolgus monkeys were exposed to PFOA at doses up to 30/20 mg/kg-day (see Appendix 2).

Yang, in a series of studies, exposed C57BL/6 mice to PFOA at a level of 0.02% (about 30 mg/kg-day) in the diet for 7-10 days. Yang (Yang, Xie & Depierre, 2000) reported reduced body weights (≤17%), increased relative liver weights (≤136%), and decreased relative thymus and spleen weights (≤83% and ≤23%, respectively). Yang (Yang, Xie, Eriksson, Nelson & DePierre, 2001) also reported liver weight changes and increased acyl-CoA oxidase activity that occurred prior to thymus and spleen weights. It was also reported that thymus and spleen weights, and total thymus and spleen cell counts, returned to within control following a period of 5-10 days after cessation of PFOA in the diet.

Yang (Yang, Xie, Alexson, Dean Nelson & DePierre, 2002a) reported that splenic IgM and IgG-producing cells were reduced in male C57BL/6 mice fed a diet containing about 30 mg/kg-day for 10 days. Serum levels of anti-HRBC IgM and IgC1 antibodies were significantly decreased compared with controls. Immunosupression was also observed in splenic lymphocytes from PFOA-treated mice to T-and B-cell specific activators ConA and lipopolysaccharide. When splenic lymphocytes were treated in vitro, this inhibition was not observed.

Loveless (Loveless, Hoban, Sykes, Frame & Everds, 2008) treated CD-1 mice and Sprague-Dawley rats to PFOA at doses of 0, 0.3, 1, 10, or 30 mg/kg-day over a period of 28 days via gavage.

Histopathologic analyses were conducted of the spleen, thymus, and lymph nodes. For rats, PFOA did not affect production of anti-SRBC antibodies, even with decreased body weight gain and increased serum corticosterone in a few rats exposed at 10 and 30 mg/kg-day. In mice, systemic toxicity and stress were observed at exposure levels of 10 and 30 mg/kg-day. Liver weight-adjusted body weights were increased as were serum corticosterone levels over controls. Neutrophils and monocytes were increased in mice; absolute lymphocyte numbers were decreased at exposure levels of 10 and 30 mg/kg-day. The liver was the major organ of toxicity in both rats and mice. At ≥1 mg/kg-day and ≥10 mg/kg-day, absolute and relative liver weights were significantly increased in rats. This correlated with increased hepatocellular hypertrophy. In mice, liver weights and hepatocellular hypertrophy were significantly increased at ≥0.1 mg/kg-day; individual cell and focal necrosis at ≥1 mg/kg-day; and increased mitotic figures and bile duct hyperplasia at ≥10 mg/kg-day.

DeWitt (Dewitt, Copeland, Strynar & Luebke, 2008) reported using C57BL/6 mice administered PFOA via gavage at 0 or 30 mg/kg-day over 15 days or 10 days followed by administration of the vehicle for 5 days. It was observed that SRBC-specific IgM antibody titers decreased about 20% in both the recovery and constant PFOA-treated mice vs. controls. SRBC-specific IgG titers and delayed-type hypersensitivity were not affected. In addition to the gavage study, C57BL/6N mice were treated with 0 to 30 mg/kg-day PFOA in drinking water for 15 days in two dose regimes. In the first, with doses of 0, 3.75, 7.5, 15, or 30 mg-kg-day, SRBC-specific IgM antibody titers decreased 11% and 29% at treatment levels of 3.75 and 30 mg/kg-day, respectively. In the second dose regime, with doses of 0, 0.94, 1.88, 3.75, or 7.5 mg/kg-day, SRBC-specific IgM antibody titers decreased about 7% relative to controls at treatment levels of 3.75 and 7.5 mg/kg-day, respectively. A NOAEL was established at 1.88 mg/kg-day.

DeWitt (DeWitt, Copeland & Luebke, 2009a) treated adrenalectomized or sham-operated C57BL/6N mice with 0, 3.75, 7.5, 15, or 30 mg/kg body weight. IgM antibody titers decreased 15% in sham mice and 18% in adrenalectomized mice. This indicates that adrenalectomy is not protective against immunosuppression. In sham mice, cortisone concentrations were significantly increased at 30 mg/kg, but these levels decreased to insignificance 5 days after exposure ended. No increase in cortisone concentration was observed in adrenalectomized mice. This indicates immune response to PFOA is not dependent of serum cortisone concentration.

PFOA appears to affect some elements of the immune system, however adverse effects on immune function have yet to be demonstrated. It may be that effects observed are stress-related.

Animal Studies – Genotoxicity

Numerous studies of the genotoxicity of PFOA have been reported (Hazleton Inc., 1995a; Hazleton Inc., 1995b; Hazleton Inc., 1996a; Hazleton Inc., 1996b; Hazleton Inc., 1996c; Hazleton Inc., 1996d;

Hazleton Inc., 1996e; Litton Bionetics, 1978; Notox, 2002; Stone Research Laboratories, 1981; Toxicon, 2002). PFOA did not induce DNA mutations in bacteria and yeast with or without metabolic activation; did not induce forward mutations in CHO cells; and did not significantly increase chromosomal aberrations in human lymphocytes. In CHO cells, PFOA did induce chromosomal aberrations and polyploidy both in the presence of and in the absence of metabolic activation in one of two tests. Tardiff (Tardiff et al., 2009) concluded that these results are confounded by the high level of cytotoxicity of PFOA towards CHO cells. In the second of these tests, no significant increases of chromosomal aberrations were observed both with and without metabolic activation, except at a single dose level with metabolic activation that also produced cytotoxicity. PFOA was inactive in a mouse *in vivo* bone marrow micronucleus assay.

Human Studies

There is a wealth of epidemiological and surveillance studies reported in the literature over the past 10-20 years, including those conducted in the U.S., Europe, and Asia. Tardiff (Tardiff et al., 2009) provided a current summary (see Appendix 3). These studies do not provide evidence for a causal association between PFOA exposure and the development of cancer in the general population. Several studies have reported cancers associated with occupational exposure to PFOA (for example, bladder and prostate cancer, melanoma: (Alexander, Olsen, Burris, Mandel & Mandel, 2003; Gilliland & Mandel, 1993); male reproductive and gastro-intestinal tract neoplasms (Olsen, Burlew, Hocking, Skratt, Burris & Mandel, 2001)). Follow-up studies failed to establish an association between cancer incidence and PFOA exposure in workers (Alexander, 2001; Alexander & Olsen, 2007; Grice, Alexander, Hoffbeck & Kampa, 2007). Lundin & Alexander (2007) reported no association between pancreatic cancer and PFOA exposure when comparing the test cohort with the general population, but did report a significant increase between exposed and non-exposed workers.

Selection of Key Studies and Critical Endpoints – Noncancer Effects

The NCSAB has selected two key studies on which to base a recommendation for an IMAC for PFOA. Because human studies have not demonstrated a quantifiable dose-response relationship between PFOA exposure and health effects, the NCSAB elected to rely on animal studies.

Butenhoff, 2004

This is a two-generation rat study (Butenhoff et al., 2004b) in which male and female Sprague-Dawley rats were dosed orally with 0, 1, 3, 10, or 30 mg/kg the ammonium salt of PFOA. Current EPA OPPTS 870.3800 guidelines were followed. The critical endpoint selected was the ratio of liver to brain weight in F_0 and F_1 rats (LOAEL = 1 mg/kg-day).

Butenhoff, 2002

This is a 6-month study (Butenhoff et al., 2002) in which groups of male cynomolgus monkeys were treated by mouth with 0, 3, 10, 30 (reduced to 20) mg/kg-day APFO in capsule form. The critical endpoint selected was the ratio of liver to brain weight (LOAEL = 3 mg/kg-day).

Selection of Key Studies and Critical Endpoints – Cancer Effects

Sibinski, 1987

This study was described in the Chronic/Cancer Studies section. Groups of male and female Sprague-Dawley rats (Crl:CD BR) were fed diets containing 0, 30 or 300 ppm APFO for two years. An additional group consisting of 15 males and 15 females were fed diets of 0 or 300 ppm APFO and sacrificed and evaluated at one year. The critical effect selected as the point of departure (POD) is incidence of testicular tumors (NOAEL = 1.3 mg/kg-day).

Quantitative Assessment

Butenhoff, 2004

Butenhoff (Butenhoff et al., 2004c) reported the following data for the critical endpoint of liver-to-brain weight ratio in F_0 and F_1 male rats (Butenhoff et al., 2004b):

Table 6 - Reported Liver-to-Brain Weight Ratio in Male Rats Treated with PFOA (Butenhoff et al., 2004c)

Liver/Brain Wt. Ratio	Oral Gavage Dose (mg/kg-day)				
	0	1	3	10	30/20
Generation					
F_0	9.0 ± 1.2 (30)	10.7 ± 1.5 (30)	12.3 ± 1.2 (30)	12.8 ± 1.8 (30)	12.5 ± 1.4 (29)
F_1	9.3 ± 1.4 (30)	10.8 ± 1.5 (29)	12.2 ± 1.8 (30)	12.9 ± 1.6 (30)	13.6 ± 1.7 (29)

Dose was converted to an equivalent serum level using a regression equation (R^2 = 0.993) to estimate area under the curve (AUC) (µg-hr/mL) from oral dose for male rats (Butenhoff, 2004c):

$$AUC\left(\frac{\mu g - hr}{mL}\right) = 1019.6 \times oral\ dose\left(\frac{mg}{kg - day}\right)$$

Dividing the AUC by 24-hours yields an average serum concentration over a 24-hour dosing interval. Since there is a long half-life of PFOA in humans, this is an appropriate average concentration metric.

Using Benchmark Dose Software (v 2.1 R52), a linear model, and eliminating the two highest doses, a Benchmark Internal Concentration ($BMIC_{10}$) and its lower bound ($LBMIC_{10}$) for F_0 and F_1 male rats were determined as shown in Table 7:

Table 7. Results of the Benchmark Internal Concentration and Its Lower Bound Calculation based on Butenhoff et al., 2004c data
((BMRF: The benchmark response factor; AIC: Akaike Information Criterion)

Generation	$BMIC_{10}$	$LBMIC_{10}$	BMRF	p	AIC
	µg/mL	µg/mL			
F_0	58	48	1.1	0.05	143
F_1	79	62	1.1	0.14	175

Since the NCSAB uses a central estimate value for a chronic endpoint, the lesser of the two central estimates, $BMIC_{10}$ = 58 µg/mL, was selected as a conservative POD.

Butenhoff, 2002

Butenhoff (Butenhoff et al., 2002) reported a 6-month study in which groups of male cynomolgus monkeys were treated by mouth with APFO in capsule form. The critical endpoint selected was the ratio of liver to brain weight:

Table 8 - Reported Liver-to-Brain Weight Ratio in Male Cynomolgus Monkeys Treated with APFO (Butenhoff et al., 2002)

Oral Dose (mg/kg-day)	0	3	10	30/20
Serum PFOA level (µg/mL)	0.16 ± 0.15 (4)*	72 ± 47 (4)	85 ± 20 (4)	155 ± 102 (2)
Liver/Brain Wt.	0.934 ± 0.074 (4)*	1.34 ± 0.23 (4)	1.30 ± 0.23 (4)	1.22 ± 1.2 (2)

*mean ± SD (sample size)

Serum PFOA levels reported were from samples at weeks 20, 22, 24, and 26.

The data (serum PFOA level and liver/brain weight) in Table 8, when modeled using Benchmark Dose software (v 2.1 R52), a linear model, highest dose level discarded, constant variance, BMRF = 1.1, yielded a $BMIC_{10}$ estimate of 40 µg/mL (p = 0.39), that was selected as the POD for study.

Sibinski, 1987

For a cancer endpoint, (Tardiff et al., 2009) used a physiologically-based toxicokinetic model (Tan et al., 2008) with the Sibinski data to estimate an $LBMIC_{10}$ of 203 µg/mL PFOA in plasma. Since this value is a lower bound and on the order of 10 times that of any of the other PODs, it is the opinion of the NCSAB that an IMAC based on any of the other key studies will be protective of cancer in humans. Therefore, it is not necessary to proceed further with this endpoint.

Uncertainty Factors

To the points of departure enumerated above, the NCSAB will apply the following uncertainty factors (Table 9):

Table 9 – Uncertainty Factors Selected by NC SAB for PFOA Noncancer Risk Assessment

Uncertainty Factor	Value	Rationale
Interspecies (animal-to-human)	3	PFOA is not metabolized in humans. Half-life in humans is much greater than for rodents. Humans are likely to be less sensitive to toxic properties of PFOA than rodents.
Intraspecies (average human-to-sensitive human)	10	To account for sensitive human subpopulations.
Study Type (subchronic-to-long term)	1	There is little discernable difference in serum levels at which effects have been reported in subchronic and chronic studies.
LOAEL-to-NOAEL	1	$BMIC_{10}$ values used to estimate a NOAEL
Database Completeness	1	The PFOA database is extensive with studies in 3 species, including acute, subchronic, and chronic studies. In addition, there are genotoxicity studies, as well as reproductive, developmental, and immunotoxicity studies.
Total Uncertainty Factor	**30**	

Table 10 summarizes the critical endpoints of each key study as well as the estimate of a resulting IMAC:

Table 10 – Maximum Allowable Concentration Estimations for PFOA based on the Critical Endpoints of Key Studies

Key Study	POD, µg/mL	Exposure Level[a], µg/person-day	UF	IMAC estimate[b], µg/L
	58	487.2	30	1.6
Butenhoff, 2002 (monkey)	40	336.0	30	1.1

a. Exposure Level = POD (µg/mL) x 0.12 µg ingested/kg/µg/mL x 70 kg/person. The 0.12 µg ingested/kg/µg/mL factor is from (Clewell et al., 2006)

b. IMAC Estimate = (Exposure Level/UF) x 0.2/2 L/person-day. A Relative Source Contribution factor of 20% (0.2) and a daily consumption factor of 2L were used

Other Assessments of PFOA in Water

Minnesota

Minnesota has established a "Health Risk Limit" (HRL) for PFOA in drinking water (Minnesota Department of Health, 2008). The basis for the HRL was a 6-month cynomolgus monkey study by (Butenhoff et al., 2002). A $BMDL_{10}$ of 23 mg/L was used as the POD. Using a one-compartment model and assuming a PFOA half-life of 1387 days in humans and a volume of distribution of 0.2 L/kg, a human equivalent dose (HED) was determined to be 0.0023 mg/kg-d. Using a total uncertainty factor of 30 (3 toxicodynamic portion of animal-to-human, 10 sensitive individuals), a relative source contribution of 0.2, and an intake rate of 0.053 L/kg-d (95% upper limit for adults, equivalent to 3.7 L/d), the HRL was determined to be 0.3 µg/L, or 0.3 ppb.

NOTE: using an intake rate of 2 L/d and a BMD_{10} (central estimate) of 40 mg/L , as is used in North Carolina (shown in Table 12), the HRL becomes 0.9 µg/L (0.9 ppb).

New Jersey

New Jersey established a "Guidance Level" for PFOA in drinking water (Post, Louis, Cooper, Boros-Russo & Lippincott, 2009). The basis for this level was a chronic diet study in adult female rats (Sibinski, 1987). The endpoint used was decreased body weight. A NOAEL of 1.6 mg/kg-d was reported. An animal serum level at the NOAEL of 1800 µg/L was determined based on AUC. An uncertainty factor of 100 (10 animal-to-human, 10 sensitive individual) was used to determine a "target human serum level" of 18 µg/L. Using a relative source contribution factor of 0.2, a "target contribution to human serum from drinking water" was determined to be 4 µg/L. It was further assumed that there is a 100-fold concentration factor of PFOA in humans from drinking water (Emmett et al., 2006b), so the PFOA concentration in drinking water corresponding to a target contribution to human serum was determined to be 0.04 µg/L .

North Carolina

The Division of Public Health (DPH) of the North Carolina Department of Health and Human Services developed a Public Health Goal (NCPHG) for PFOA based on a PBPK model developed by (Clewell et al., 2006). Using the PBPK model adjusted for a human half-life of 3.8 years, (Butenhoff et al., 2002) cynomolgus monkey data, an endpoint of increased liver weight, and a POD ($LBMIC_{10}$) of 23 µg/L PFOA in serum, DPH determined a human equivalent administered dose to be 2.75×10^{-3} mg/kg-d. Applying a total uncertainty factor of 30 (3 for toxicodynamics, 10 for intraspecies), a 70-kg adult body weight, 20% relative source contribution, and a intake level of 2L/day, yielded a PFOA concentration in water of 0.63 µg/L (0.63 ppb). This is the NCPHG for PFOA. NCPHGs are not regulatory levels but provide guidance of acceptable contaminant levels in private wells, whereas IMACs are regulatory levels in ground water established by DWQ.

Recommendation

It is the recommendation of the NCSAB to the Division of Water Quality that the Interim Maximum Allowable Level (IMAC) for PFOA in groundwater be reduced to 1 µg/L (ppbv).

Appendix 1 **PFOA Concentration (ng/mL, ppb) in Human Fluids (Lau et al., 2007)**

PFOA Mean is a geometric mean. Those values with an asterisk (*) are arithmetic means

Location	Demographic	Sample Type	Year of Collection	Number of Samples	PFOA Mean[a]	PFOA Range	References
Los Angeles, CA	Adults	Serum	2001	125	4.1	2.1–34.1	(Olsen et al., 2003a)
Boston, MA	Adults	Serum	2001	109	5.4	1.5–13.9	(Olsen et al., 2003a)
Mpls–St Paul, MN	Adults	Serum	2001	100	4.5	1.9–20.0	(Olsen et al., 2003a)
Charlotte, NC	Adults	Serum	2001	96	6.3	2.1–29.0	(Olsen et al., 2003a)
Portland, OR	Adults	Serum	2001	107	3.6	2.1–16.7	(Olsen et al., 2003a)
Hagerstown, MD	Adults	Serum	2001	108	4.2	2.1–52.3	(Olsen et al., 2003a)
Seattle, WA	Elderly adults	Serum	2001	238	4.2	1.4–16.7	(Olsen et al., 2004a)
23 US States	Children (2–12 years)	Serum	1994–1995	598	4.9	1.9–56.1	(Olsen et al., 2004b)
Washington Co., MD	Adults	Serum	1974	178	2.1	NR	(Olsen, Huang, Helzlsouer, Hansen, Butenhoff & Mandel, 2005)
Washington Co., MD	Adults	Plasma	1989	178	5.5	NR	(Olsen et al., 2005)
Kentucky	Adult females	Serum	2000	46	4.7*	<3–7.3	(Kannan et al., 2004)
Michigan	Adult males	Serum	2000	29	5.7*	<3–14.7	(Kannan et al., 2004)
Kentucky	Adult females	Whole blood	2002	11	23*	15–39	(Kannan et al., 2004)
Kentucky	Adult males	Whole blood	2002	19	41.6*	11.0–88	(Kannan et al., 2004)
New YorkCity	Adults	Plasma	2002	70	27.5*	14–56	(Kannan et al., 2004)
Atlanta, GA	Adult females	Serum	2003	10	4.2*	0.2–10.0	(Kuklenyik, Reich, Tully, Needham & Calafat, 2004)
Atlanta, GA	Adult males	Serum	2003	10	5.56*	2.8–10.4	(Kuklenyik et al., 2004)
Atlanta, GA	Adult females	Breast milk	2003	2			(Kuklenyik et al., 2004)
United States	Non-Hispanic White	Serum	1999–2000	529	5.6	NR	(Calafat, Kuklenyik, Reidy, Caudill, Tully & Needham, 2007a)
United States	Non-Hispanic Black	Serum	1999–2000	309	4.8	NR	(Calafat et al., 2007a)
United States	Mexican-American	Serum	1999–2000	584	3.9	NR	(Calafat et al., 2007a)
United States	Non-Hispanic White Female	Serum	2001–2002	13 pooled	4.0*	NR	(Calafat, Kuklenyik, Caudill, Reidy & Needham, 2006a)
United States	Non-Hispanic Black Female	Serum	2001–2002	6 pooled	2.9*	NR	(Calafat et al., 2006a)
United States	Mexican-American Female	Serum	2001–2002	8 pooled	2.1*	NR	(Calafat et al., 2006a)
United States	Non-Hispanic White Male	Serum	2001–2002	13 pooled	7.0*	NR	(Calafat et al., 2006a)
United States	Non-Hispanic Black Male	Serum	2001–2002	6 pooled	3.6*	NR	(Calafat et al., 2006a)
United States	Mexican-American Male	Serum	2001–2002	7 pooled	2.9*	NR	(Calafat et al., 2006a)
United States	Adults	Serum	1990–2002	23 pooled	9.6	2.8–23.7	(Calafat et al., 2006b)
St Paul, MN	Adult females	Plasma	2005	20	2.3*	0.7–4.7	(Olsen et al., 2006b) (Olsen et al., 2007a)
St Paul, MN	Adult males	Plasma	2005	20	2.6*	0.7–4.2	(Olsen et al., 2006b) (Olsen et al., 2007a)
St Paul, MN	Adult females	Serum	2000	50	5.1*	1.4–20.0	(Olsen et al., 2006b) (Olsen et al., 2007a)
Southeastern OH	Adults and children	Serum	2005	371	354*	NR	(Emmett et al., 2006b)

Ottawa, Gatineau, Canada	Adult females	Serum	2002	21	3.08*	< 1.2–6.1	(Kubwabo, Vais & Benoit, 2004)
Ottawa, Gatineau, Canada	Adult males	Serum	2002	35	3.6*	< 1.2–7.2	(Kubwabo et al., 2004)

Appendix 2 Summary of Subchronic Studies, see (Tardiff et al., 2009), Table 2

Species/Study Type	Number/Sex/Dose	Dose Level	Results	Reference
Oral				
Mouse 14-day feeding	5(M/F)	10-10,000 ppm	Mortality (100%) at ≥3000 ppm; mortality at 1000 ppm; ↑liver weight/body weight ≥30 ppm. **LOAEL = 30 ppm.**	(DuPont Company, 1981) cited in (Kennedy et al., 2004)
Mouse 14-day feeding	5(M/F)	0, 30, 300, or 3000 ppm	Mortality (100%) at 3000 ppm; ↓body weight and 1/5 females died at 300 ppm; ↑liver weights at ≥30 ppm. No histopathology. **LOAEL = 30 ppm.**	(Kennedy, 1987)
Mouse 21-day feeding	5(M/F)	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, or 30 ppm	↑liver weights at ≥3 ppm. No histopathology. **LOAEL = 1 ppm.**	(Kennedy, 1987)
Mouse 28-day feeding	5(M/F)	0, 30, 100, 300, 1000, 3000, 10,000, or 30,000 ppm	Mortality (100% or close to) at ≥300 ppm; ↓body weights throughout study (100 ppm males and females); ↓body weight in week 4 (30 ppm females);↑liver weights (30 and 100 ppm males and females); panlobar diffuse hepatocellular hypertrophy accompanied by focal to multifocal cytoplasmic lipid vacuoles in 30 ppm and 300 ppm animals. **LOAEL = 30 ppm.**	(Griffith et al., 1980)
Rat 7-day feeding	4-6(M)	0.0025, 0.005, 0.01, 0.02, or 0.04% (w/w)	↑triglycerides in liver (all doses) but ↓serum cholesterol, total phospholipids, anf phosphatidylcholine (only given in 0.02% dose), ↑liver glycerolipids (all doses).	(Kudo et al., 1999)
Rat 28-day feeding	5(M/F)	0, 30, 100, 300, 1,000, 3,000, 10,000, or 30,000 ppm	Mortality (100%) at 10,000 and 30,000 ppm; weight loss (males: ≥30 ppm; females: 3,000 ppm); ↑liver weights (males: ≥30 ppm; females: ≥1,000 ppm). Liver effects: hepatocellular hypertrophy, hepatocyte degeneration and/or necrosis; focal bile duct proliferation. **LOAEL = 30 ppm.**	(Griffith et al., 1980)
Rat 90-day feeding	5(M/F)	0, 10, 30, 100, 300, or 1,000 ppm	Weight loss and ↑liver weight at 300 and 1,000 mg/kg. Liver effects: hepatocellular hypertrophy, hepatocyte degeneration and/or necrosis; focal bile duct proliferation. **LOAEL/NOAEL cannot be determined.**	(Griffith et al., 1980)
Rat 13-week feeding	45-55(M)	0, 1, 10, 30, or 100 ppm	↑hepatic palmitoyl CoA activity (30 and 100 ppm); ↑absolute and relative liver weights and hepatocellular hypertrophy (≥1 mg/kg); effects were reversible after 8-week recovery period; no treatment- related effects on serum hormone levels. **NOAEL = 100 ppm (6.5 mg/kg-day).**	(Palazzolo, 1993; Perkins, 1992) as cited in Tardiff
Rat 28-day gavage	10(M)	0, 5, or 20 mg/kg-day	↓body weights (20 mg/kg-day); ↑relative liver, kidney and gonad weights (both doses); hepatocyte hypertrophy with cytoplasmic vacuolation (both doses); congestion and thickened epithelial walls in lung (both doses); turbidness and tumefaction in kidney proximal convoluted tubular epithelium (20 mg/kg). **LOAEL = 5 mg/kg-day.**	(Cui, Zhou, Liao, Fu & Jiang, 2009)
Rhesus monkey 90-Day Gavage	2 (M/F)	0,10,30,100,300, or 1,000 mg/kg-day	Mortality (100% at weeks 2-5) at 100 mg/kg-day; mortality (1M and 2F at weeks 7-12) and ↓body weight at 300 mg/kg (M); atrophy of lymphoid tissues at ≥30 mg/kg; **NOAEL = 10 mg/kg-day.**	(Griffith et al., 1980)
Cynomolgus Monkey 60-Day Gavage	4 or 6 (M)	0,3,10, or 30 (reduced to 20) mg/kg-day	↑Liver weights at all dose levels; body weight loss at 30/20 mg/kg. LOAEL = 3 mg/kg-day	(Butenhoff et al., 2002)
Inhalation				
Rat 10-day Exposure	24(M)	0,1,8, or 84 mg/m^3	Two died at 84 mg/m^3 and weight loss that recovered by Day 16; ↑Liver weight, serum alkaline phosphatase, hepatocellular hypertrophy, and necrosis at ≥8 mg/m^3; all liver effects reversible by end of 42-day recovery period. **NOAEL = 1 mg/m^3**	(Kennedy, Hall, Brittelli, Barnes & Chen, 1986)
Rat 10 Applications	15(M)	20,200, or 2000mg/kg (6 h/day, 5 days/week)	Skin irritation and reversible reduction in body weights at ≥200 mg/kg (persistent body weight loss at 2000 mg/kg); ↑liver weight, serum AST and ALT levels, hepatocellular hypertrophy and necrosis (≥20 mg/kg), **LOAEL = 20 mg/kg.**	(Kennedy, 1985)
Rabbits 10 Applications	10(M/F)	100 mg/kg (6 h/day for 2 weeks)	Reversible reduction in body weight but elevated blood fluorine levels throughout the recovery period.	(Riker, 1981)

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Appendix 3 - Summary of Human Studies, see (Tardiff et al., 2009), Table 1

Location	Cancer and Mortality	Morbidity	Measures	Outcome
Occupational Epidemiology				
Alabama; Decatur	(Olsen et al., 2001) [Retrospective cohort; Decatur chemical plant compared to Decatur film plant - observed to expected 'episodes of care'; N = 652 SI: gastrointestinal neoplasms, reproductive tract neoplasms, benign colonic polyps] (Alexander et al., 2003) [cohort; N= 2,083 SI: bladder and other urinary cancer mortality with high exposure; association uncertain] (Alexander et al., 2007) [cohort, N = 1,400 NS: bladder cancer mortality] (Grice et al., 2007) [cohort, N = 1,400 NS: melanoma, prostate cancer]	(Olsen, Burris, Berlew & Mandel, 2003c) [Cross-sectional analysis compared with Antwerp population and PFOS serum quartiles; longitudinal analysis; N = 263] (Olsen et al., 2001) [Retrospective cohort; Decatur chemical plant compared to Decatur film plant - observed to expected 'episodes of care'; N = 652] [N = 24] (Olsen et al., 2007b) [Comparison of Decatur (medium serum PFOA), Antwerp (low serum PFOA) and Cottage Grove (high serum PFOA) data; N = 506] (Grice et al., 2007) [cohort, N = 1,400]	Hematology, clinical chemistry, thyroid hormone, urinalysis Health claim records Self-reported renal disease and symptoms Clinical chemistry, thyroid hormones, liver enzymes Self-reported symptoms, medical reports	SI: cholesterol, triglycerides (dose response with PFOA not determined) NS: high-density cholesterol; bilirubin, hepatic enzymes (GGT, AST, ALT); thyroid hormones SI: acute cholelithiasis, cystitis, urinary tract infections, menopausal and menstrual disorders, benign colonic polyps (dose-response not determined) NS SI: alkaline phosphatase, total bilirubin (negative association), ALT, GGT (no dose response); Triglycerides NS: HDL, LDL, thyroid hormones NS: Cystitis, bladder calculi, colon polyps, cholelithiasis, cholecystitis, liver disease, gastric ulcer, benign prostatic hyperplasia, prostatitis, birth weight
Minnesota; Cottage Grove	(Gilliland et al., 1993) [cohort comparing PFOA production to no production, N = 3,537 SI: prostate cancer mortality] (Alexander, 2001) [cohort, N = 3,992 NS: prostate cancer mortality] (Lundin et al., 2007) [cohort comparing definitely PFOA exposed to non-exposed, N = 3,993 SI: prostate cancer mortality - within PFOA exposed cohort; NS: prostate cancer mortality- general population; NS: 19 other cancer sites - general population;	(Gilliland & Mandel, 1996) [cross-sectional analysis; N = 115] (Olsen, Burris, Burlew & Mandel, 2000) [cross-sectional analysis; N = 165] (Olsen, Butenhoff & Mandel, 2003d) [medical surveillance; N = 148] (Olsen, Gilliland, Burlew, Burris, Mandel & Mandel, 1998) [2 cross-sectional analyses; N = 111	Hepatic enzymes., LDL, HDL, cholesterol Hepatic enzymes, LDL, HDL, cholesterol Hematology, clinical chemistry; thyroid hormone analysis, self- reported symptoms Hormones (estradiol, testosterone, prolactin, thyroid hormones, cortisol, LH, FSH, DHEAS, 17-HP, SHBG)	NS NS NS NS

	SI: cerebrovascular disease mortality- within PFOA exposed cohort; NS: cerebrovascular disease mortality – general population]	and 80] (Olsen et al., 2007b) [Comparison of Cottage Grove (high serum PFOA), Antwerp (low serum PFOA) and Decatur (medium serum PFOA) data; N = 506]	Clinical chemistry, thyroid hormones, liver enzymes	NS: high-density cholesterol, low density cholesterol; triglycerides, thyroid hormones; hepatic enzymes
West Virginia; Washington Works	(Leonard, 2003) [surveillance; cohort comparing workers (1957- 2000) to reference population, N = 5,523 SI - bladder cancer (males); kidney cancer (males), mortality due to heart disease; NS: leukemia, multiple myeloma, prostate, colorectal cancer] (Karns & Fayerweather, 1991) [case-control of 9 leukemia cancer cases NS: leukemia] Leonard et al. (2008) [cohort compared with reference regional worker population, N = 6,027 NS: mortality due to malignant neoplasms; SI: mortality due to diabetes mellitus; NS: mortality due to ischemic heart disease, respiratory disease, kidney disease] (Walrath & Burke, 1989) [case-control of 9 leukemia cases in employees from 1956-1989 NS: leukemia]	(DuPont Company, 2005) [health study, N = >1,000] Sakr et al. (2007a) [cross-sectional analysis, N = 1,025] Sakr et al. (2007b) [longitudinal analysis, N = 454]	Hematology, urinalysis, liver function Clinical chemistry, hematology Clinical chemistry, hematology	SI: LDL NS: HDL, liver function SI: cholesterol (total choloesterol, LDL, very low-density lipoproteins, GGT) - no reported increase in cardiac risk NS: HDL, bilirubin, AST, ALT SI: total bilirubin (negative association), AST, total cholesterol NS: triglycerides, LDL, HDL
Belgium; Antwerp	NA	Olsen et al. (2003c) [cross-sectional analysis compared with Decatur population and PFOS serum quartiles; longitudinal analysis; N = 255] Olsen and Zobel (2007) [Comparison of Antwerp (low serum PFOA) with Cottage Grove (high serum PFOA) and Decatur (medium serum PFOA) data; N = 506]	Hepatic enzymes, clinical chemistry, thyroid hormone Clinical chemistry	SI: cholesterol, triglycerides NS: high-density cholesterol; bilirubin, hepatic enzymes (GGT, AST, ALT); thyroid hormones SI: triglycerides NS: high-density cholesterol, low density cholesterol, thyroid hormones; hepatic enzymes
Italy; Miteni	NA	(Costa, Sartori & Consonni, 2007) [N not specified] (Costa, Sartori & Consonni, 2009)	hepatic enzymes, HDL, LDL, cholesterol; liver, kidney & prostate functions	SI: cholesterol NS: all other measures SI: total cholesterol, uric acid, bilirubin

		[Surveillance of exposed workers versus matched non-exposed workers and versus entire plant, N = 34 active workers in two analyses, 56 active/retired workers in third analysis]		(negative association) NS: all other measures
Ohio; southeastern area [general population not occupationally exposed]	NA	Emmett et al. (2006a) [Residential exposure from drinking water; N = 371] Fletcher et al. (2009) [Residential exposure from drinking water; N = 56,351]	Hepatic enzymes, liver & kidney function, cholesterol, thyroid stimulating hormone Immune biomarkers	NS SA: decreased IgA, increased IgE (females only), increased total antinuclear antibodies
New York State [general population - anglers]	NA	(Bloom, Kannan, Spliethoff, Tao, Aldous & Vena, 2010) [subsample of cohort, N = 31]	Thyroid hormone function (TSH and free thyroxine)	NS
Developmental / Reproductive Epidemiology				
Maryland; Baltimore [general population]	NA	Apelberg et al. (2007b) [cross-sectional, N = 293 singleton births]	Fetal growth indicators	SA: head circumference, ponderal index, birth weight NS: birth length, duration of gestation
Ohio; Washington County [general population]	NA	Nolan et al. (2009) [cross-sectional study; N = 1,619 births) (Steenland et al., 2009a) [cohort, N = not given]	Birth weight, duration of gestation Pregnancy outcome, low birth weight, birth defects	**NS** **NS**
Canada [general population]	NA	(Monroy et al., 2008) [nested analysis; N = 101 pregnant women, 105 umbilical cord samples]	Birth weight	NS
Denmark [general population]	(Eriksen et al., 2009) [prospective cohort with no previous cancer diagnosis at enrollment, N = 1,240 cancer patient (772 in comparison group) NS: prostate, bladder, pancreatic, and liver cancer]	Fei et al. (2007) [cohort, N = 1,400] Fei et al. (2008a) [cohort, N = 1,400] Fei et al. (2008b) [cohort, N = 1,400] Fei et al. (2009) [cohort, N = 1,400] (Joenson, Bossi, Leffers, Astrup, Skakkebaek & Jorgenson, 2009) [cohort, N = 105]	Fetal growth indicators Fetal growth indicators Developmental milestones Fecundity Semen quality and reproductive hormones	SA: birth weight NS: preterm birth, low birth weight, small-for-gestation age NS: placental weight, head circumference, abdominal circumference, birth length NS: Apgar score, developmental milestone SA: increased time-to-pregnancy NS
Japan; Sapporo [general population]	NA	(Washino et al., 2009) [hospital-based prospective study; N = 428]	Birth weight and size	NS

SI = significant increase; **SA** = significant association; **NS** = no significant increase; **N** = number of individuals in study; **ALT** = alanine 1 aminotransferase; **AST** = aspartate aminotransferase; **GGT** = gamma glutamyl transferase, **HDL** = high-density lipoprotein; **LDL** = low-density 2 lipoprotein; **LH** = luteinizing hormone; **FSH** = follicular stimulating hormone; **17-HP** = 17 -hydroxyprogesterone; **SHBG** = sex hormone-binding 3 globulin; **DHEAS** = dehydroepiandrosterone sulfate; **NA** = not applicable

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